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A non-exercise testing method for estimating cardiorespiratory fitness: associations with all-cause and cardiovascular mortality in a pooled analysis of eight population-based cohorts

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Aims Cardiorespiratory fitness (CRF) is a key predictor of chronic disease, particularly cardiovascular disease (CVD), but its assessment usually requires exercise testing which is impractical and costly in most health-care settings. Non-exercise testing cardiorespiratory fitness (NET-F)-estimating methods are a less resource-demanding alternative, but their predictive capacity for CVD and total mortality has yet to be tested. The objective of this study is to examine the association of a validated NET-F algorithm with all-cause and CVD mortality.

Methods and results The participants were 32 319 adults (14 650 men) aged 35–70 years who took part in eight Health Survey for England and Scottish Health Survey studies between 1994 and 2003. Non-exercise testing cardiorespiratory fitness (a metabolic equivalent of VO_2max) was calculated using age, sex, body mass index (BMI), resting heart rate, and self-reported physical activity. We followed participants for mortality until 2008. Two thousand one hundred and sixty-five participants died (460 cardiovascular deaths) during a mean 9.0 [standard deviation (SD) = 3.6] year follow-up. After adjusting for potential confounders including diabetes, hypertension, smoking, social class, alcohol, and depression, a higher fitness score according to the NET-F was associated with a lower risk of mortality from all-causes (hazard ratio per SD increase in NET-F 0.85, 95% confidence interval: 0.78–0.93 in men; 0.88, 0.80–0.98 in women) and CVD (men: 0.75, 0.63–0.90; women: 0.73, 0.60–0.92). Non-exercise testing cardiorespiratory fitness had a better discriminative ability than any of its components (CVD mortality *c*-statistic: NET-F = 0.70–0.74; BMI = 0.45–0.59; physical activity = 0.60–0.64; resting heart rate = 0.57–0.61). The sensitivity of the NET-F algorithm to predict events occurring in the highest risk quintile was better for CVD (0.49 in both sexes) than all-cause mortality (0.44 and 0.40 for men and women, respectively). The specificity for all-cause and CVD mortality ranged between 0.80 and 0.82. The net reclassification improvement of CVD mortality risk (vs. a standardized aggregate score of the modifiable components of NET-F) was 27.2 and 21.0% for men and women, respectively.

Conclusion The CRF-estimating method NET-F that does not involve exercise testing showed consistent associations with all-cause and cardiovascular mortality, and it had good discrimination and excellent risk reclassification improvement. As such, it merits further attention as a practical and potentially and useful risk prediction tool.

Keywords Epidemiology • Non-exercise testing • Cardiorespiratory fitness • Cardiovascular disease • Physical activity • Health Survey for England

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Introduction

Cardiorespiratory fitness (CRF) is a measure of the capacity of the cardiovascular system to transport oxygen and the ability of the muscles to use it.[1] Low CRF has repeatedly been shown to predict increased cardiovascular disease (CVD) risk independently of conventional risk factors such as hypertension, hyperlipidaemia, obesity, and smoking.[2–8] Furthermore, CRF estimated through exercise testing has been shown to significantly improve classification of both short- and long-term risk for CVD mortality when added to traditional risk factors, such as age, systolic blood pressure, diabetes mellitus, total cholesterol, and smoking.[9] However, unlike conventional risk factors, CRF is not currently a routinely assessed component of individual risk assessment in primary care. This may be due to practical issues because the measurement of CRF, even by submaximal exercise test (e.g. indirect calorimetry during a graded exercise test), requires trained staff and the use of specialist exercise equipment and is time-consuming. Submaximal exercise tests without the measurement of gas exchange are also burdening for the patient and require the use of specialized equipment such as bicycle ergometers or treadmills that are rarely available in health-care settings. Dynamic tests without equipment, such as bleep tests[10] and the 6 min walk test,[11] are more feasible but nevertheless require supervised exercise for the patient.[12]

An international group of experts, by expanding on previous developmental and evaluation work in this area of research,[13] have developed a *non-exercise* testing cardiorespiratory fitness (NET-F) assessment method.[14] It is inherently a cost-effective method and highly feasible because all variables proposed for the estimation of NET-F are either routinely available [gender, age, body mass index (BMI), resting pulse rate] or relatively easy to obtain (self-reported physical activity) in a primary care setting. While the new NET-F-estimating method has been shown to have good concurrent validity against exercise testing-estimated CRF,[14,15] crucially, its predictive ability for outcomes that have previously been shown to be linked to CRF (all-cause and CVD mortality) has yet to be tested.

The aim of the present analyses is to examine the associations between NET-F with CVD and all-cause mortality and to assess the extent to which any association is independent of the constituent components of NET-F, BMI, resting heart rate, and self-reported physical activity.

Methods

Study sample and design

Details of the sample design and selection can be found elsewhere.[16,17] In brief, participants were drawn from the Health Survey for England (HSE) and the Scottish Health Survey (SHS)—a series of independent cohort studies with baseline examinations in 1994 (HSE only), 1995 (SHS only), 1998, 1999 (HSE only), 2003, and 2004 (HSE only). The two surveys are run by the same research agencies (Joint Health Surveys Unit) and have identical methodologies. The two studies are general population-based, sampling individuals living in households in each country. HSE and SHS samples were selected using a multistage, stratified, probability design to give a representative sample of the target populations. Stratification was based on geographical areas and not on individual characteristics: postcode (zip code) sectors were selected at the first stage and household addresses selected at the second stage. Ethical approval had been granted for all aspects of these studies by the Local Research Ethics Councils prior to each survey year data collection.

Participants in this study were aged 35–70 years at study induction. In the present analyses, we included cohort members with complete data on NET-F and conventional risk factors, and those who were free of doctor-diagnosed CVD [coronary heart disease (CHD), stroke, angina] at baseline. Seventy years was chosen as the upper age limit because the NET-F method[14] was developed using a 20- to 70-year old sample.[18]

Clinical characteristics

Height and weight were measured by trained interviewers using standard protocols.[16,17]

Computer-assisted personal interviewing modules assessed respondents' demographics, health status and history of disease, and health behaviours. Psychological health was evaluated using the General Health Questionnaire 12 (GHQ, 12-item version).[19,20] In a separate visit, qualified nurses collected information on prescribed medication and measured respondent's resting heart rate (RHR) three times following 5 min of seated rest using an Omron 907 monitor (Omron Corporation, Japan). The RHR was computed as the average of the second and third reading. Cardiovascular medication was defined using the British National Formulary[21] classification and it included positive inotropic drugs, anti-arrhythmics, diuretics, β-blockers, angiotensin-converting enzyme-inhibitors, calcium-channel blockers, nitrates, anticoagulants, antiplatelets, and lipid-regulating drugs. Physical activity questions[22,23] included the frequency (number of days in the last 4 weeks) and duration (minutes per day) of participation in domestic activity (e.g. housework, DIY, gardening, restoration work), brisk walking and cycling for any purpose, and any recreational exercise of moderate-to-vigorous intensity[24] (e.g. swimming, aerobics, callisthenics, gym exercises, team sports, racket sports). The criterion validity of the physical activity questionnaire has been demonstrated in a study on 106 English adults from the general population (45 men) where the output of accelerometers (worn for two non-consecutive weeks over a month period) was compared with responses to these questions.[25]

Non-exercise testing cardiorespiratory fitness

Non-exercise testing cardiorespiratory fitness estimates were converted into maximal aerobic capacity metabolic equivalent (MET) values such that one MET corresponded to an oxygen consumption of 3.5 mL/kg/min (based on a 70 kg man aged 40 years).[26] Out of the three NET-F algorithms developed originally,[14] we selected the algorithm that was developed in a UK population (the National Fitness Survey[18]). The criteria for this selection were both pragmatic (similarity of the National Fitness Survey and HSE/SHS populations) and statistical [in preliminary receiver operating characteristic (ROC) analyses, we found the best predictive ability for this algorithm against mortality]. The algorithm was calculated as follows:

$$\text{NET}-\text{F} = [\text{sex coefficient} \times 2.78 - (\text{age} \times 0.11) - (\text{BMI} \times 0.17) - (\text{RHR} \times 0.05) + (\text{physical activity level coefficient}) + 21.41]$$

The sex coefficient was 1 for men and 0 for women. All physical activity variables were converted into weekly frequency. The physical activity level was based on the weekly frequency of 30 min sessions of

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Table 1 Participant baseline characteristics by quartiles of estimated non-exercise testing cardiorespiratory fitness[a]

Characteristic	Quartiles of NET-F									
	Men				*P*-value[b]	Women				*P*-value[b]
	Bottom (MET < 9.8)	2nd (9.8–10.9)	3rd (10.9–12.1)	Top (>12.1)		Bottom (MET < 6.8)	2nd (6.8–8.1)	3rd (8.1–9.3)	Top (>9.3)	
n	3663	3662	3663	3662		4415	4416	4415	4420	
Age (years), mean (SD)	60.4 (7.0)	54.0 (7.7)	46.5 (6.8)	40.6 (4.9)	<0.001	60.3 (7.7)	54.3 (7.8)	47.2 (6.9)	40.9 (5.0)	<0.001
Social class (% manual)	57.2	50.8	48.4	46.6	<0.001	52.5	46.2	43.2	37.7	<0.001
Smoking (% current/ex-smoker)	71.2	67.1	62.4	51.7	<0.001	55.3	54.2	55.9	51.2	<0.001
Diagnosed diabetes (%)	7.0	2.6	2.1	0.9	<0.001	5.8	1.8	1.2	0.4	<0.001
Diagnosed hypertension (%)	32.9	24.5	14.7	8.9	<0.001	37.2	22.7	14.6	7.2	<0.001
Long-standing illness (%)	58.0	49.5	40.8	33.5	<0.001	61.4	48.8	40.3	33.0	<0.001
Psychological distress (%)	11.5	12.0	12.4	12.9	0.269	16.0	15.8	18.7	18.9	<0.001
Cardiovascular medication (%)	27.0	15.3	7.5	3.1	<0.001	33.8	17.3	9.4	3.2	<0.001
BMI (kg/m^2), mean (SD)	30.2 (4.6)	27.6 (3.7)	26.7 (3.2)	24.7 (2.8)	<0.001	31.9 (5.9)	27.4 (4.2)	25.7 (3.5)	23.2 (2.7)	<0.001
Moderate-to-vigorous physical activity (sessions/week), mean (SD)	1.5 (2.4)	2.5 (3.3)	3.1 (3.5)	4.9 (4.6)	<0.001	1.6 (2.3)	2.5 (3.0)	3.0 (3.4)	4.4 (4.2)	<0.001
Resting heart rate (b.p.m.), mean (SD)	76.2(12.1)	70.5 (11.0)	69.0 (10.0)	63.9 (9.1)	<0.001	76.1 (11.3)	72.5 (10.3)	71.3 (9.7)	68.0 (8.8)	<0.001

[a]The Health Survey for England and Scottish Health Survey cohorts. Men and women aged 35–70 years with no doctor-diagnosed CVD (CHD, angina, stroke) at baseline.
[b]Based on likelihood ratio χ^2 test (categorical variables) or one-way ANOVA (continuous variables); testing null hypothesis of no difference between quartiles.

intense domestic activity, walking (of moderate intensity only), and 15 min sessions of vigorous sports and exercises (including vigorous cycling). The physical activity scale coefficients were categorized into four levels as follows. Level 1: inactive (no physical activity of any intensity reported), coefficient = 0.0; Level 2: regular domestic physical activity only or <1.5 sessions of moderate-to-vigorous physical activity (MVPA)/week, coefficient = 0.35; Level 3: 1.5 to <3 MVPA sessions/week, coefficient = 0.29; Level 4: 3–6 MVPA sessions/week, coefficient = 0.64; Level 5: >6 MVPA sessions/week, coefficient = 1.21. The above algorithm has shown a multiple correlation of $r = 0.76$ (standard error of estimate: 1.97 MET) against exercise testing-estimated CRF and a high level of cross-validity ($r = 0.71$–0.80) when applied in samples other than the one it was developed.[14]

Mortality follow-up

Participants were flagged by the British National Health Service (NHS) Central Registry, who notified us of the date and cause of death where applicable. Diagnoses for the primary cause of death was based on the *International Classification of Diseases*, Ninth (ICD-9) and Tenth (ICD-10) Revisions. Codes corresponding to CVD mortality were 390-459 for ICD-9 and I01-I99 for ICD-10.

Data handling and statistical analysis

Due to marked sex differences in NET-F levels, all results were presented for men and women separately. Study participants' characteristics are presented by NET-F quartiles, and differences across quartiles were tested using χ^2 tests (categorical variables) or one-way analysis of variance (continuous variables). We calculated age-standardized absolute risk rates (per 10 000 participants) for all-cause and CVD mortality by NET-F quartiles. With no major violation of the proportional hazards assumption evident, the Cox regression model was used, with months as the time scale, to estimate the risk of mortality according to the NET-F category. Surviving participants were censored at 31 December 2008 (SHS cohorts) or 15 February 2008 (HSE cohorts). Hazard ratios were computed as per SD increase in NET-F. All Cox models were adjusted for age, social class (based on the Registrar General's social occupational classification[27] which is grouped as follows: professional, managerial and technical, skilled non-manual, skilled manual, partly-skilled, unskilled/routine occupations), smoking (light smoker, heavy smoker, ex-smoker, non-smoker), anti-hypertensive and other cardiovascular medication, GHQ12 score, doctor-diagnosed diabetes, and long-standing illness when appropriate. Sensitivity analyses excluded participants who died during the first 36 months of follow-up to reduce the likelihood of reverse causation. To compare the relative predictive value of NET-F and each of its modifiable constituent components (BMI, resting heart rate, physical activity), we constructed ROC curves with corresponding areas under the curve (AUC). The AUC (also known as *c*-statistic) is equal to the probability that a classifier will rank a randomly chosen positive instance higher than a randomly chosen negative one (0.50 = risk prediction by pure chance) and 95% confidence intervals (CIs) separately for all-cause and CVD mortality. To compare the relative discriminant ability of the NET-F and the aggregate of its modifiable constituent components (BMI, RHR, MVPA), we used existing methods[28] to develop a continuous clustered score. After *z*-score conversion [z = (value − mean)/standard deviation (SD)] of these three constituent component variables, the three *z* scores were summed and the sum was divided by 3 to compile this score with units of SD. For MVPA (which is protective for mortality risk), the *z* scores were multiplied by −1.

Using standard methods,[29] we further assessed discrimination by calculating the proportion of all-cause and CVD deaths that occurred in the bottom quintile of the NET-F score (i.e. sensitivity of the highest risk quintile of predicted risk for identifying deaths) and the proportion of individuals without events who are not in the bottom quintile of the test (i.e. specificity of the highest risk quintile for deaths). To assess calibration, we calculated model-predicted risk of all-cause and CVD mortality for each NET-F quintile and compared these values to observed mortality risk per quintile. For the observed risk, we used the Kaplan–Meier-derived mean cumulative hazard functions. For the predicted risk, we used the calculated mean cumulative hazard function from the (fully-adjusted) Cox models. We compared the net reclassification for CVD mortality risk between tertiles of the NET-F algorithm and tertiles of the aggregate standardized (but unweighted) score of the modifiable NET-F components we described above.[30] We calculated the net reclassification improvement (NRI) for using a previously described formula[31]:

$$\mathrm{NRI} = P(\mathrm{up}|\mathrm{event}) - P(\mathrm{down}|\mathrm{event}) + P(\mathrm{down}|\mathrm{non-event}) - P(\mathrm{up}|\mathrm{non-event})$$

where P is the proportion of participants moving up or down in terms of predicted risk category.

All analyses were performed using SPSS version 17 (IBM Inc.) and all tests of statistical significance were based on two-sided probability ($P < 0.05$).

Results

Out of the 59 401 participants (26 595 men) aged 35–70 years who were initially considered, 7214 (12.1%) did not consent to their record being linked to mortality data or were lost to follow-up; 3810 reported doctor-diagnosed CVD and were excluded. Among the remaining 48 542 participants, NET-F for 14 591 could not be calculated owing to missing data for resting heart rate ($n = 13\,103$), and/or BMI ($n = 3515$) information, and/or another at least one other covariable ($n = 1399$). Compared

Table 2 Hazard ratios for the association between non-exercise testing cardiorespiratory fitness[a] and all-cause mortality[b]

	HR per 1 standard deviation increase in NET-F (95% CI)	*P*-trend value
Men ($n = 14\,650$/1194 deaths)		
Age-adjusted model	0.75 (0.69–0.82)	<0.001
Fully adjusted model[c]	0.85 (0.78–0.93)	<0.001
Women ($n = 17\,669$/971 deaths)		
Age-adjusted model	0.82 (0.75–0.90)	<0.001
Fully adjusted model[c]	0.88 (0.80–0.98)	0.014

[a]NET-F is a weighted score computed using BMI, resting heart rate, physical activity, age, and sex.
[b]Men and women aged 35–70 years with no doctor-diagnosed CVD (CHD, angina, stroke) at baseline.
[c]Adjusted for social class, smoking, anti-hypertensive and other cardiovascular medication, psychological distress, hypertension, diabetes, long-standing illness.

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Table 3 Hazard ratios for the association between non-exercise testing cardiorespiratory fitness[a] and cardiovascular mortality[b]

	HR per 1 standard deviation increase in NET-F (95% CI)	*P*-trend value
Men ($n = 14\,650$/277 CVD deaths)		
Age-adjusted model	0.65 (0.54–0.77)	<0.001
Fully adjusted model[c]	0.75 (0.63–0.90)	0.002
Women ($n = 17\,669$/183 CVD deaths)		
Age-adjusted model	0.65 (0.53–0.80)	<0.001
Fully adjusted model[c]	0.73 (0.60–0.92)	0.007

[a]NET-F is a score computed based on age, sex, BMI, resting heart rate and physical activity level.
[b]Men and women aged 35–70 years with no doctor-diagnosed CVD (CHD, angina, stroke) at baseline.
[c]Adjusted for social class, smoking, anti-hypertensive and other cardiovascular medication, psychological distress, hypertension, diabetes, long-standing illness.

with those included, the excluded from the analysis sample were slightly older (51.9 vs. 50.5 years) and more likely to be male (48.6 vs. 45.4%), from manual social class (48.3 vs. 46.1%), ex-smokers (34.2 vs. 30.8%), on CVD medication (30.1 vs. 14.6%), and report doctor-diagnosed hypertension (79.6 vs. 69.8%) and long-standing illness (54.3 vs. 49.6%) (all $P < 0.001$). The resulting 32 319 individuals comprised the core data set (14 650 men) of the present study. There was a total of 288 988 person-years at risk for the 9.0 ($\pm$ 3.6) years of average follow-up. A total of 2165 deaths (1194 among men) occurred during the follow-up, of which 460 were due to CVD causes (277 among men).

Table 1 presents the characteristics of the sample by the NET-F quartile. In both men and women, NET-F was inversely associated with age, smoking, (manual) social class, doctor-diagnosed hypertension and diabetes, anti-hypertensive and other cardiovascular medication, long standing illness, BMI, and resting heart rate, and directly associated with MVPA. The mean NET-F was 10.9 ($\pm$ 1.6) for men and 8.0 ($\pm$ 1.7) for women. Supplementary material online, *Figure S1*, presents the distribution of NET-F values in men and women. There was a clear gradient in age-standardized absolute risk for any cause and CVD death among both men

Table 4 Discrimination statistics of the non-exercise testing cardiorespiratory fitness[a] algorithm estimates[b]

	Men		Women	
	All-cause mortality	CVD mortality	All-cause mortality	CVD mortality
Area under the curve (95% CIs)[c]	0.73 (0.71–0.74)	0.73 (0.71–0.76)	0.70 (0.68–0.71)	0.74 (0.71–0.77)
Sensitivity[d]	0.44	0.49	0.40	0.49
n (events/bottom quintile)	527/2921	137/2921	382/3517	89/3517
Specificity[e]	0.82	0.81	0.81	0.80
n (non-events/four top quintiles)	11 026/11 688	11 548/11 688	13 484/14 066	13 973/14 066

[a]NET-F is a weighted score computed using BMI, resting heart rate, moderate-to-vigorous physical activity, age, and sex.
[b]Men ($n = 14\,650$) and women ($n = 17\,669$) aged 35 to 70 years with no doctor-diagnosed CVD (CHD, angina, stroke) at baseline.
[c]Calculated from inverted NET-F.
[d]Calculated as the proportion of events captured by the bottom (highest risk) NET-F quintile.
[e]Calculated as the proportion of non-events captured by the top four NET-F quintiles.

Table 5 Receiver-operator characteristic area under the curve for the potentially modifiable constituent components of the non-exercise testing cardiorespiratory fitness[a]

Predictor	AUC (95% CI)			
	Men		Women	
	All-cause mortality	CVD mortality	All-cause mortality	CVD mortality
Resting heart rate	0.61 (0.59–0.62)	0.59 (0.56–0.63)	0.57 (0.55–0.59)	0.60 (0.56–0.64)
Body mass index	0.45 (0.43–0.47)	0.59 (0.46–0.53)	0.50 (0.47–0.52)	0.52 (0.48–0.56)
MVPA[b] (inverse coding)	0.60 (0.58–0.61)	0.60 (0.56–0.63)	0.62 (0.60–0.63)	0.64 (0.60–0.68)
Standardized aggregate score[c]	0.58 (0.57–0.60)	0.60 (0.57–0.63)	0.59 (0.57–0.61)	0.64 (0.60–0.68)

[a]Men ($n = 14\,650$) and women ($n = 17\,669$) aged 35–70 years with no doctor-diagnosed CVD (CHD, angina, stroke) at baseline.
[b]Moderate-to-vigorous physical activity
[c]This score includes measures of BMI, resting heart rate, and moderate-to-vigorous physical activity. After *z*-score conversion [z = (value − mean)/SD], the three *z*-scores were summed and the sum was divided by 3 to compile a score with units of SD. For moderate-to-vigorous physical activity (which is protective for mortality risk), the *z*-score was multiplied by −1.

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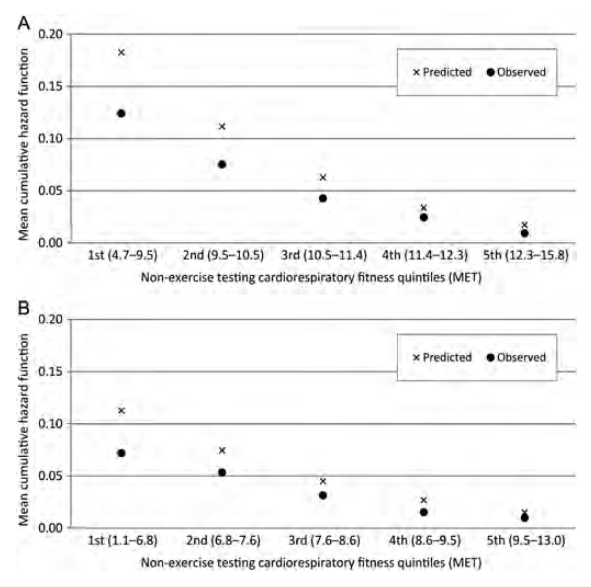

Figure 1 Calibration by quintile of non-exercise testing cardiorespiratory fitness (a weighted score computed using BMI, resting heart rate, physical activity, age, and sex) score for men (*A*) and women (*B*) for all-cause mortality risk. The observed values correspond to the Kaplan–Meier cumulative hazard; predicted values correspond to the Cox model-derived cumulative hazard.

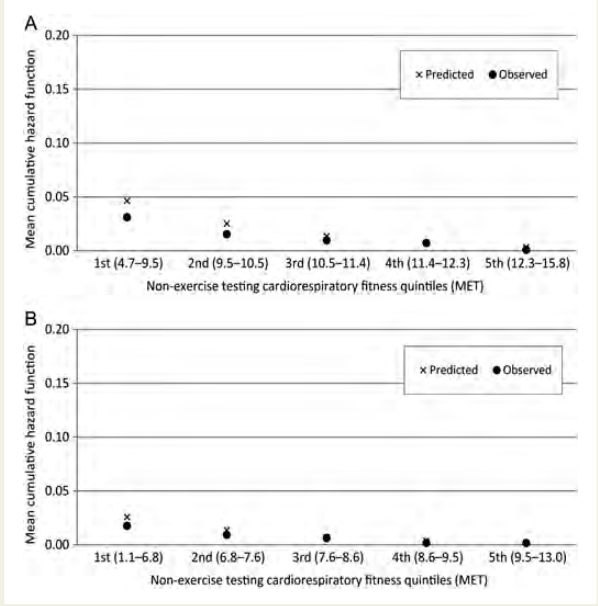

Figure 2 Calibration by quintile of non-exercise testing cardiorespiratory fitness (a weighted score computed using BMI, resting heart rate, physical activity, age, and sex) score for men (*A*) and women (*B*) for cardiovascular disease mortality risk. The observed values correspond to the Kaplan–Meier cumulative hazard; predicted values correspond to the Cox model-derived cumulative hazard.

and women (see Supplementary material online, *Figures S2* and *S3*). Higher NET-F was associated with lower all-cause mortality among both men and women (*Table 2*). Although these associations were attenuated following adjustments for potential confounders, they did remain statistically significant. There was also an association between higher NET-F and lower CVD mortality which persisted following adjustments for potential confounders (*Table 3*). In general, the Cox model hazard ratios per SD increase in NET-F were lower for men than for women. Excluding deaths from any cause (or CVD deaths) occurring in the first 36 months of follow-up did not appreciably change the results (see Supplementary material online, *Table S1*).

Table 4 presents the discrimination statistics for NET-F for all-cause and CVD mortality. The AUC for all-cause mortality was comparable between men [e.g. the *c*-statistic = 0.73 (95% CI: 0.71–0.74)] and women [0.70 (0.68–0.71)], and the same was true for CVD mortality as an outcome. Non-exercise testing cardiorespiratory fitness (*Table 4*) demonstrated appreciably greater discriminative ability (based on the AUC) than any single component variable or the aggregate score of its modifiable constituent components (*Table 5*). The sensitivity of the NET-F algorithm to predict events occurring in the highest risk quintile was better for CVD (0.49 in both sexes) than all-cause mortality (0.44 and 0.40 for men and women, respectively). The specificity was comparable across all gender by outcome groups (range: 0.80–0.82).

Figures 1 and *2* show the mean predicted vs. observed risk for all-cause and CVD mortality, respectively, by fifths of NET-F. For both men and women, the all-cause mortality plots show a tendency for over-prediction for those participants in the lowest NET-F quintiles. The CVD mortality plots showed fair calibration for both men and women, although there is a tendency to over-predict CVD deaths among participants in the lowest NET-F quintiles. *Table 6* presents the reclassification statistics for CVD mortality. Compared with the aggregate score of its potentially modifiable constituent components, NET-F reclassified risk correctly (i.e. to a category of higher risk) 25.6% of men and 20.2% of women who had a fatal CVD event. The overall NRI was excellent at 27.2% for men and 21.0% for women (both $P < 0.001$).

Discussion

To our knowledge, this is the first study to examine the associations of the NET-F-estimating method with mortality and one of the few to study non-exercise testing-estimated fitness in general. In this population sample of 35- to 70-year olds, NET-F was consistently associated with all-cause and CVD mortality with minor gender differences. The reductions in mortality risk associated with increased NET-F are comparable to those reported in other studies that looked at the associations between exercise testing-estimated CRF and mortality. For example, a meta-analysis of 33 studies (~85 000 individuals)[26] found that the relative risk reduction associated with 1 MET increase in CRF was 13% (95% CI: 10–16%) for all-cause mortality and 15% (12–18%) for CVD events. In our study, a 1 SD increase in NET-F (corresponding to 1.6–1.7 MET) was associated with a 15% (7–22%) and a 12% (2–20%) decrease in risk for death

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Table 6 Reclassification of the predicted risk of cardiovascular mortality of men and women, on the basis of the non-exercise testing cardiorespiratory fitness algorithm vs. the standardized unweighted aggregate score of its modifiable components[a]

Tertiles of standardized aggregate score[a]	Tertiles of NET-F[b]			Increased risk	Decreased risk	Net correctly reclassified (%)
	Bottom (highest risk)	Middle	Top (lowest risk)			
Men						
CVD death cases ($n = 277$)						
Bottom (lowest risk)	15	28	13	97	26	25.6
Middle	54	25	12			
Top (highest risk)	116	12	2			
Controls (no CVD death) ($n = 14\,332$)						
Bottom (lowest risk)	433	1341	3039	3108	3338	1.6
Middle	1334	1930	1516			
Top (highest risk)	2917	1534	288			
Net reclassification index[c]	27.2% ($P < 0.001$)					
Women						
CVD death cases ($n = 183$)						
Bottom (lowest risk)	7	14	5	59	22	20.2
Middle	38	19	7			
Top (highest risk)	77	15	0			
Controls (no CVD death) ($n = 17\,486$)						
Bottom (lowest risk)	412	1731	3720	3726	3863	0.8
Middle	1583	2404	1838			
Top (highest risk)	3773	1706	319			
Net reclassification index[c]	21.0% ($P < 0.001$)					

[a]This score includes measures of BMI, resting heart rate, and moderate-to-vigorous physical activity. After z-score conversion [$z = (\text{value} - \text{mean})/\text{SD}$], the three z scores were summed and the sum was divided by 3 to compile a score with units of SD. For moderate-to-vigorous physical activity (which is protective for mortality risk), the z scores were multiplied by -1.
[b]NET-F is a weighted score computed using BMI, resting heart rate, physical activity, age, and sex.
[c]Calculated as NRI = [P(up|event) − P(down|event) + P(down|non-event) − P(up|non-event)] × 100, where P is the proportion of participants moving up or down in terms of the predicted risk category.

from any cause and a 25% (10–33%) and a 27% (8–40%) decrease in risk for CVD death in men and women, respectively.

Studies looking at the associations between other non-exercise CRF estimates and mortality are scarce. The Women's Ischemia Syndrome Evaluation (WISE) study[32] evaluated CRF using a self-reported measurement that assessed the ability to perform various activities; this measurement had previously been found to correlate with exercise testing-estimated CRF.[33] Each 1-MET increase in estimated CRF was associated with an 8% (11–15%) decrease in risk of major CVD events among ~1000 women during the average 4-year follow-up.[32] Although this level of relative risk reduction is considerably lower than that conferred by our NET-F measurement, the WISE study results also support the potential of non-exercise CRF estimation methods for CVD death risk prediction at a population level. In another study of 858 men followed up over 16.5 years, self-rated fitness was at least as good a predictor of mortality as self-reported health, and men reporting poor fitness were at three times the elevated risk of death.[34]

We found that NET-F had considerably higher predictive ability compared with any of its modifiable constituent components alone or their standardized aggregate score (as judged by the *c*-statistic). This suggests that NET-F is a superior risk prediction method when compared with RHR, physical activity, or BMI alone or jointly in terms of both all-cause and CVD-specific mortality. The excellent NRI that NET-F demonstrated (>27% for men and 21% for women), which was mainly due to considerable improvements in the classification of the CVD cases, provides further evidence on the superiority of NET-F over its unweighted modifiable components in terms of CVD death risk prediction. It is noteworthy that the discriminative ability of NET-F (*c*-statistic for CVD death: 0.73–0.75) is comparable to the *c*-statistics of 0.74–0.77 for the Framingham risk prediction model,[35] a score which is used worldwide to make decisions about preventive interventions, such as lipid-lowering treatment, lifestyle intervention recommendations, and aspirin use.[36,37] Overall, these findings suggest that NET-F estimates are robust predictors of overall and CVD-specific mortality, and may be considered for incorporation into the medical examination routine of physicians and preventive cardiologists.

Although this study supports the predictive value of NET-F at a population level, it does not give any information on the utility of

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the method as a means of assessment of CRF changes during fitness programmes. Further, it does not give information on the classification agreement between NET-F and actual (measured) CRF or exercise testing-estimated CRF. Furthermore, it remains unknown whether changes in intervention-induced improvements in NET-F will be translated into improvements in the outcomes (e.g. CHD events). These are questions that can optimally be answered using controlled trial designs, although such studies would require large sample sizes and relatively long follow-up.

The key strengths of our study included the large population sample and number of events that allowed us to take generous measures to reduce the chances of reverse causation (e.g. exclude deaths occurring in the first 3 years of follow-up), and the availability of a broad range of potential confounders that we took into account in our multivariable models. There are also some caveats to the findings reported here. Our analyses are based on a cohort comprising mainly white Europeans so it is unknown if the results are generalizable to other ethnic groups. We were unable to consider changes in NET-F over time as there was only one baseline measurement of the variables required for the computation of the algorithm. Like the conventional exercise testing-based methods, NET-F cannot capture the genetic component of CRF. Our analyses are limited to fatal CVD events because we had only mortality as an outcome for the whole data set. The participants excluded from our study due to missing data might have introduced bias into the analyses. Lastly, the most heavily weighted variable (physical activity) was the only component of the algorithm that was assessed using subjective methods (self-reports), which might have introduced bias and noise into the results. Perhaps, an NET-F method containing an objectively assessed physical activity component (measured by e.g. pedometers or accelerometers) would have been an even more powerful predictor of mortality but it is unlikely that such assessments are feasible and practical in most clinical settings.

In conclusion, our findings from a large population-based study suggest that the NET-F-estimating method may be a useful novel tool to predict cardiovascular and overall mortality in adults. Further research is needed to examine the feasibility, cost-effectiveness, and incremental predictive value of this test in routine clinical practice.

Details of ethical approval

This research complies with the Declaration of Helsinki. Consent was obtained from Health Survey for England participants for their data to be used in medical research prior to data collection. Ethical approval had been granted for all aspects of these studies by the Local Research Ethics Councils prior to each survey year data collection.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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References

1. Laukkanen JA, Kurl S, Salonen JT. Cardiorespiratory fitness and physical activity as risk predictors of future atherosclerotic cardiovascular diseases. *Curr Atheroscler Rep* 2002;**4**:468–476.
2. Blair SN, Kohl HW, Paffenbarger RS, Clark DG, Cooper KH, Gibbons LW. Physical fitness and all-cause mortality. *JAMA* 1989;**262**:2395–2401.
3. Berry JD, Willis B, Gupta S, Barlow CE, Lakoski SG, Khera A, Rohatgi A, de Lemos JA, Haskell W, Lloyd-Jones DM. Lifetime risks for cardiovascular disease mortality by cardiorespiratory fitness levels measured at ages 45, 55, and 65 years in men: The Cooper Center Longitudinal Study. *J Am Coll Cardiol* 2011; **57**:1604–1610.
4. Laukkanen JA, Rauramaa R, Salonen JT, Kurl S. The predictive value of cardiorespiratory fitness combined with coronary risk evaluation and the risk of cardiovascular and all-cause death. *J Intern Med* 2007;**262**:263–272.
5. Myers J, Prakash M, Froelicher V, Do D, Partington S, Atwood JE. Exercise capacity and mortality among men referred for exercise testing. *N Engl J Med* 2002;**346**:793–801.
6. Gulati M, Pandey DK, Arnsdorf MF, Lauderdale DS, Thisted RA, Wicklund RH, Al-Hani AJ, Black HR. Exercise capacity and the risk of death in women—The St James Women Take Heart Project. *Circulation* 2003;**108**:1554–1559.
7. Mora S, Redberg RF, Sharrett AR, Blumenthal RS. Enhanced risk assessment in asymptomatic individuals with exercise testing and Framingham risk scores. *Circulation* 2005;**112**:1566–1572.
8. Kokkinos P, Myers J, Kokkinos JP, Pittaras A, Narayan P, Manolis A, Karasik P, Greenberg M, Papademetriou V, Singh S. Exercise capacity and mortality in black and white men. *Circulation* 2008;**117**:614–622.
9. Gupta S, Rohatgi A, Ayers CR, Willis BL, Haskell WL, Khera A, Drazner MH, de Lemos JA, Berry JD. Cardiorespiratory fitness and classification of risk of cardiovascular disease mortality. *Circulation* 2011;**123**:1377–1383.
10. Stevens N, Sykes K. Aerobic fitness testing: an update. *Occup Health* 1996;**48**: 436–438.
11. Zugck C, Krüger C, Dürr S, Gerber SH, Haunstetter A, Hornig K, Kübler W, Haass M. Is the 6-minute walk test a reliable substitute for peak oxygen uptake in patients with dilated cardiomyopathy? *Eur Heart J* 2000;**21**:540–549.
12. Garber CE, Blissmer B, Deschenes MR, Franklin BA, Lamonte MJ, Lee I-M, Nieman DC, Swain DP. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. *Med Sci Sports Exerc* 2011;**43**:1334–1359.
13. Jackson AS, Blair SN, Mahar MT, Wier LT, Ross RM, Stuteville JE. Prediction of functional aerobic capacity without exercise testing. *Med Sci Sports Exerc* 1990; **22**:863–870.
14. Jurca R, Jackson AS, LaMonte MJ, Morrow JR, Blair SN, Wareham NJ, Haskell WL, van Mechelen W, Church TS, Jakicic JM, Laukkanen R. Assessing cardiorespiratory fitness without performing exercise testing. *Am J Prev Med* 2005;**29**:185–193.

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15. Mailey E, White S, Wojcicki T, Szabo A, Kramer A, McAuley E. Construct validation of a non-exercise measure of cardiorespiratory fitness in older adults. *BMC Public Health* 2010;**10**:59–67.
16. Joint Health Surveys Unit. *The Health Survey for England 2008. Volume 2: Methods and Documentation*. Leeds: The Information Centre for Health and Social Care; 2009. www.ic.nhs.uk/pubs/hse08physicalactivity (20 December 2010).
17. The Scottish Executive. *The Scottish Health Survey 2003*. Edinburgh: The Scottish Executive; 2005. http://www.scotland.gov.uk/Publications/2005/11/25145024/50251 (20 May 2011).
18. Activity and Health Research. *Allied Dunbar National Fitness Survey: Main Findings*. London: Sports Council and Health Education Authority; 1992.
19. Goldberg DP, Gater R, Sartorius N, Ustun TB, Piccinelli M, Gureje O, Rutter C. The validity of two versions of the GHQ in the WHO study of mental illness in general health care. *Psychol Med* 1997;**27**:191–197.
20. Hamer M, Molloy GJ, Stamatakis E. Psychological distress as a risk factor for cardiovascular events: pathophysiological and behavioral mechanisms. *J Am Coll Cardiol* 2008;**52**:2156–2162.
21. British National Formulary. *BNF version 60*. London: British National Formulary; 2010.
22. Stamatakis E, Hamer M, Lawlor DA. Physical activity, mortality and cardiovascular disease: Is domestic physical activity beneficial? The Scottish Health Survey 1995, 1998 and 2003. *Am J Epidemiol* 2009;**169**:1191–1200.
23. Stamatakis E, Hamer M, Primatesta P. Cardiovascular medication, physical activity and mortality: cross-sectional population study with ongoing mortality follow up. *Heart* 2009;**95**:448–453.
24. Ainsworth BE, Haskell WL, Whitt MC, Irwin ML, Swartz AM, Strath SJ, O'Brien WL, Bassett DR, Schmitz KH, Emplaincourt PO, Jacobs DR, Leon AS. Compendium of Physical Activities: an update of activity codes and MET intensities. *Med Sci Sports Exerc* 2000;**32**:S498–S516.
25. Joint Health Surveys Unit. *Health Survey for England Physical Activity Validation Study: Substantive Report*. Leeds: Health and Social Care Information Centre; 2007.
26. Kodama S, Saito K, Tanaka S, Maki M, Yachi Y, Asumi M, Sugawara A, Totsuka K, Shimano H, Ohashi Y, Yamada N, Sone H. Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women. *JAMA* 2009;**301**:2024–2035.
27. Szreter SRS. The genesis of the Registrar-General's Social Classification of Occupations. *Br J Sociol* 1984;**35**:522–546.
28. Stamatakis E, Hamer M, Mishra G. Early adulthood TV viewing and cardiometabolic risk profiles in early middle age: results from a population, prospective cohort study. *Diabetologia* 2012;**55**:311–320.
29. D'Agostino RB Sr, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, Kannel WB. General cardiovascular risk profile for use in primary care: The Framingham Heart Study. *Circulation* 2008;**117**:743–753.
30. Kivimaki M, Batty GD, Singh-Manoux A, Ferrie JE, Tabak AG, Jokela M, Marmot MG, Davey Smith G, Shipley MJ. Validating the Framingham Hypertension Risk Score: results from the Whitehall II Study. *Hypertension* 2009;**54**:496–501.
31. Pencina MJ, D'Agostino RB, Steyerberg EW. Extensions of net reclassification improvement calculations to measure usefulness of new biomarkers. *Stat Med* 2011;**30**:11–21.
32. Wessel TR, Arant CB, Olson MB, Johnson BD, Reis SE, Sharaf BL, Shaw LJ, Handberg E, Sopko G, Kelsey SF, Pepine CJ, Bairey Merz CN. Relationship of physical fitness vs body mass index with coronary artery disease and cardiovascular events in women. *JAMA* 2004;**292**:1179–1187.
33. Hlatky MA, Boineau RE, Higginbotham MB, Lee KL, Mark DB, Califf RM, Cobb FR, Pryor DB. A brief self-administered questionnaire to determine functional capacity (the Duke Activity Status Index). *Am J Cardiol* 1989;**64**:651–654.
34. Phillips AC, Der G, Carroll D. Self-reported health, self-reported fitness, and all-cause mortality: prospective cohort study. *Br J Health Psychol* 2010;**15**:337–346.
35. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. *Circulation* 1998;**97**:1837–1847.
36. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* 2002;**106**:3143–3421.
37. Mosca L, Banka CL, Benjamin EJ. Evidence-based guidelines for cardiovascular disease prevention in women: 2007 update. *Circulation* 2007;**115**:1481–1501.

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